Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1686–1689
Tetrahedron Letters

Tf-based sulfamide-amine alcohol-catalyzed enantioselective alkynylation of aldehydes

Hongwang Li, Yongbo Huang, Wei Jin, Feng Xue, Boshun Wan *

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, PR China

Received 8 November 2007; revised 25 December 2007; accepted 25 December 2007
Available online 10 January 2008

Abstract

A series of new chiral Tf-based sulfamide-amine alcohols (Tf-based SAA) were synthesized from natural chiral (−)-ephedrine and aziridines derived from commercially available chiral amino alcohols. Among these ligands, **3a** was found to be more effective for the addition reaction of alkynylzinc to aromatic aldehyes at room temperature without using other kinds of metal species, providing 81–92% ee and up to 99% yields.

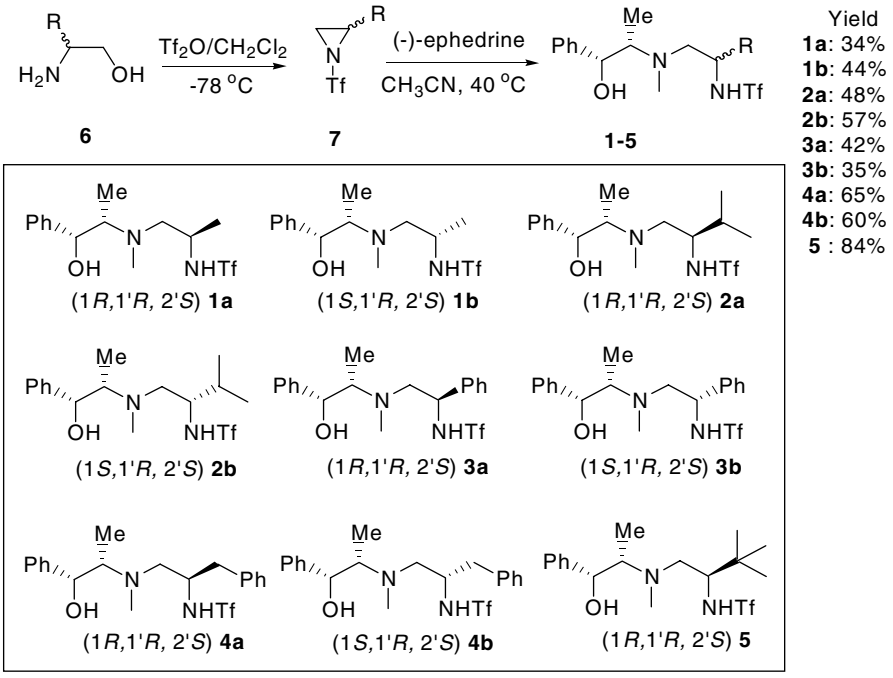
Keywords: Sulfamide-amine alcohols; Asymmetric addition; Propargylic alcohols; Alkynylation; Aldehydes

Catalytic asymmetric formation of C–C bonds is one of the most powerful methods for modern organic synthesis.[1] Enantioselective addition of terminal alkynes to carbonyl compounds is a useful approach to the preparation of chiral secondary propargyl alcohols,[2] which are important building blocks for the synthesis of many pharmaceuticals and natural products.[3] In recent years, the asymmetric addition of alkynylzinc to aldehydes was extensively studied via chiral amino alcohols,[4] BINOL and its derivatives,[5] and sulfonamides.[6] However, $Ti(O\text{–}^{i}Pr)_4$ or other metal species were usually necessary in these catalytic systems except a few chiral ligands.[7] Very recently, we reported a series of chiral Ts-based sulfamide-amine alcohol (SAA) ligands for the asymmetric diethylzinc addition to aldehydes without using the titanium complex.[8] Thereafter, we found that the catalysts were also effective for the asymmetric alkynylation of carbonyl compounds.[9] It is well known that enantioselectivities of chiral ligand-catalyzed reactions are always related to the electronic effects of ligands besides their steric effects. Considering the strongly electron-withdrawing nature of *p*-tolyl sulfonyl (Ts) in the aforesaid ligands,[10] we turned to the trifluoromethanesulfonyl (Tf), a more strongly electron-withdrawing group and a new class of Tf-based sulfamide-amine alcohols (Tf-based SAA) were prepared through two simple efficient steps (Scheme 1).[11] Herein, we report Tf-based SAA-catalyzed asymmetric addition of phenylacetylene to aldehydes in the absence of $Ti(O\text{–}^{i}Pr)_4$ at room temperature.

The new Tf-based SAA ligands were applied in the enantioselective addition of alkynylzinc to benzaldehyde in hexane (Table 1).[12] As shown, **1a**, **2a**, **3a** and **4a** derived from (*R*)-aziridines gave good enantioselectivities (Table 1, entries 1, 3, 5 and 7) and were more effective than those (**1b**, **2b**, **3b** and **4b**) derived from (*S*)-aziridines (Table 1, entries 2, 4, 6 and 8). The (*R*)-configuration of the chiral carbon linked to nitrogen of sulfamide was necessary to achieve high enantioselectivities. Interestingly, we also found a trend among ligands **1a**, **2a**, **3a** and **4a** that the catalytic enantioselectivity was higher with more sterically hindered substituting group at the chiral carbon (Table 1, entries 1, 3, 5 and 7). However, unexpectedly, ligand **5** possessing a bulkier *tert*-butyl group only provided a moderate asymmetric induction of 52% ee (Table 1, entry 9). **3a** was the most effective ligand among those Tf-based SAA ligands,

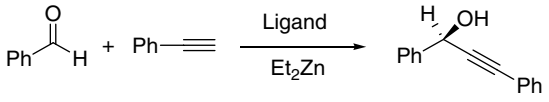
* Corresponding author. Tel.: +86 411 84379260; fax: +86 411 84379223.
E-mail address: bswan@dicp.ac.cn (B. Wan).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.131



Scheme 1. Synthesis of Tf-based sulfamide-amine alcohols.

Table 1
Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by Tf-based SAA[a,b]



Entry	Ligand	Yield[c] (%)	ee[d] (%)
1	**1a**	58	68
2	**1b**	61	2
3	**2a**	70	77
4	**2b**	63	−6
5	**3a**	92	88
6	**3b**	74	45
7	**4a**	82	76
8	**4b**	72	0
9	**5**	84	52

[a] Phenylacetylene/Et_2Zn/aldehyde/ligand = 2.0:2.0:1:0.1;1 mL hexane, 20 h.
[b] All reactions were performed under argon and at room temperature.
[c] Isolated yield.
[d] The ee values were determined by HPLC on a Chiracel OD-H column.

affording the highest asymmetric activity with 88% ee and 92% yield (Table 1, entry 5).

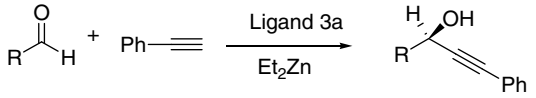
To improve the enantioselectivity, the reaction conditions, including solvent, temperature and the amount of ligand, were optimized with **3a** (Table 2). We found that the results were strongly influenced by the solvent. When the reaction was carried out in THF or Et_2O, low ee values were afforded (Table 2, entries 1 and 3). However, there was a dramatic enhancement in enantioselectivity when dichloromethane, hexane or toluene was used as the solvent (Table 2, entries 2, 4 and 5). It was found that toluene was the best solvent, and the corresponding optically active propargyl alcohol was obtained in 99% yield and 92% ee (Table 2, entry 5). When the volume of toluene was doubled, the enantioselectivity decreased slightly (Table 2, entry 6). Moreover, decreased ee values were provided at lower temperatures (Table 2, entries 7 and 8). When the amount of ligand **3a** was reduced to 5 mol %, the ee value was slightly influenced, but the yield was obviously decreased (Table 2, entry 9). Increasing the amount of ligand **3a** to 20 mol % did not have any beneficial effect (Table 2, entries 10 and 11). We also found that the reaction had been effectively completed in 16 h (Table 2, entries 11 and 12).

Table 2
Asymmetric addition of phenylacetylene to benzaldehyde using **3a** as ligand under various conditions[a,b]

Entry	**3a** (mol %)	Solvent	T (°C)	Time (h)	Yield[d] (%)	ee[e] (%)
1	10	THF	rt	20	55	14
2	10	CH_2Cl_2	rt	20	92	85
3	10	Et_2O	rt	20	90	42
4	10	Hexane	rt	20	92	88
5	10	Toluene	rt	20	99	92
6[c]	10	Toluene	rt	20	91	89
7	10	Toluene	−20	48	50	82
8	10	Toluene	0	24	50	87
9	5	Toluene	rt	24	76	86
10	20	Toluene	rt	16	99	92
11	10	Toluene	rt	16	99	92
12	10	Toluene	rt	12	90	91

[a] Phenylacetylene/Et_2Zn/aldehyde = 2.0:2.0:1; unless otherwise stated, the volume of solvent was 1 mL.
[b] All reactions were performed under argon.
[c] The volume of toluene was 2 mL.
[d] Isolated yield.
[e] The ee values were determined by HPLC on a Chiracel OD-H column.

Table 3
Asymmetric addition of phenylacetylene to aldehydes promoted by ligand **3a**[a,b]



Entry	R	Yield[c] (%)	ee[d] (%)
1	Ph	99	92
2	*o*-Me–Ph	99	90
3	*m*-Me–Ph	92	90
4	*p*-Cl–Ph	99	89
5	*m*-MeO–Ph	88	83
6	*p*-MeO–Ph	96	89
7	*o*-F–Ph	84	81
8	*m*-F–Ph	99	88
9	*p*-F–Ph	93	85
10	*m*-CF_3-Ph	75	84
11	*p*-CF_3-Ph	99	88
12	3,5-2Cl–Ph	65	84
13	1-Naphthyl	95	89
14	Cyclohexyl	84	54

[a] Phenylacetylene/Et_2Zn/aldehyde/ligand = 2.0:2.0:1:0.1; 1 mL toluene, rt, 16 h.
[b] All reactions were performed under argon and at room temperature.
[c] Isolated yield.
[d] The ee values were determined by HPLC on a Chiracel OD-H column.

Under the optimized reaction conditions (Table 2, entry 11), ligand **3a** was successfully employed to catalyze the asymmetric addition of phenylacetylene to aldehydes. As can be seen from the summarized results (Table 3), this method was highly efficient for all of aromatic aldehydes studied; the propargylic alcohols were obtained with 81–92% ee and up to 99% yield (Table 3, entries 1–13). Moreover, 54% ee for cyclohexanecarboxaldehyde was provided (Table 3, entry 14).

In summary, a class of new chiral Tf-based SAA ligands has been conveniently synthesized from commercially available starting materials in two simple steps. Tf-based SAA **3a** is a highly enantioselective and extensively practical ligand for the enantioselective alkynylation of aromatic aldehydes in the absence of $Ti(O\text{–}^iPr)_4$ at room temperature. Comparing our Ts-based SAA for this reaction of up to 84% ee,[9b] it provides a more effective practical method to produce chiral propargyl alcohols. Studies are currently underway to apply these ligands to other enantioselective catalytic reactions.

Acknowledgement

Financial support from the National Basic Research Program of China (2003CB114402) is gratefully acknowledged.

References and notes

1. (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley: New York, 2000; (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, 1999.
2. For reviews see: (a) Lu, G.; Li, Y. M.; Li, X. S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736; (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095; (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873.
3. (a) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131; (b) Fox, M. E.; Li, C.; Marino, J. P. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467; (c) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.
4. (a) Trost, B. M.; Weiss, A. H.; Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8; (b) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207; (c) Fang, T.; Du, D. M.; Lu, S. F.; Xu, J. X. *Org. Lett.* **2005**, *7*, 2081; (d) Jiang, B.; Si, Y. G. *Adv. Synth. Catal.* **2004**, *346*, 669; (e) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687; (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
5. (a) Li, Z. B.; Liu, T. D.; Pu, L. *J. Org. Chem.* **2007**, *72*, 4340; (b) Qin, Y. C.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335; (c) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760; (d) Li, X. S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636; (e) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143.
6. (a) Xu, Z. Q.; Lin, L.; Xu, J. K.; Yan, W. J.; Wang, R. *Adv. Synth. Catal.* **2006**, *348*, 506; (b) Xu, Z.; Ni, M.; Wang, R.; Han, Z. J.; Mao, B.; Da, C. S.; Liu, L.; Chen, C. *Adv. Synth. Catal.* **2005**, *347*, 1659; (c) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193; (d) Wang, R.; Xu, J.; Da, C.; Yan, W.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747.
7. (a) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901; (b) Wolf, C.; Liu, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10996; (c) Kang, Y. F.; Wang, R.; Liu, L.; Da, C. S.; Yan, W. J.; Xu, Z. Q. *Tetrahedron Lett.* **2005**, *46*, 863; (d) Li, M.; Zhu, X. Z.; Yuan, K.; Cao, B. X.; Hou, X. L. *Tetrahedron: Asymmetry* **2004**, *15*, 219; (e) Kang, Y. F.; Liu, L.; Wang, R.; Yan, W. J.; Zhou, Y. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3155; (f) Xu, M. H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555; (g) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147.
8. (a) Mao, J. C.; Wan, B. S.; Wang, R. L.; Wu, F.; Lu, S. W. *J. Org. Chem.* **2004**, *69*, 9123; (b) Mao, J. C.; Wan, B. S.; Zhang, Z. J.; Wang, R. L.; Wu, F.; Lu, S. W. *J. Mol. Catal. A: Chem.* **2005**, *225*, 33.
9. (a) Mao, J. C.; Zhang, Z. J.; Wan, B. S.; Wu, F.; Lu, S. W. *Catal. Commun.* **2006**, *7*, 550; (b) Mao, J. C.; Wan, B. S.; Wu, F.; Lu, S. W. *Chirality* **2005**, *17*, 245; (c) Mao, J. C.; Wan, B. S.; Wu, F.; Wang, R. L.; Lu, S. W. *J. Mol. Catal. A: Chem.* **2005**, *232*, 9; (d) Mao, J. C.; Wan, B. S.; Wu, F.; Lu, S. W. *J. Mol. Catal. A: Chem.* **2005**, *237*, 126.
10. Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1997**, *16*, 5130.
11. *Typical procedure for the preparation of Tf-based sulfamide-amine alcohols* (**3a**): The aziridines were synthesized according to the literature.[13] Triflic anhydride (3.6 mL, 22 mmol) was added dropwise over 1 h to a solution of (*R*)-phenylglycinol (1.37 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol) in dry dichloromethane (40 mL) under argon at −78°C, then the mixture was kept at −30 °C overnight. The reaction mixture was washed twice with chilled (0 °C) 0.1 M HCl and twice with chilled saturated aqueous Na_2CO_3. The organic phase was dried ($MgSO_4$). Without purification, the solution was added dropwise to a solution of (−)-ephedrine (1.65 g, 8 mmol) in acetonitrile at 0 °C. The resulting mixture was stirred overnight at room temperature followed by 3 days at 40 °C, and the acetonitrile was evaporated. The residue was purified by column chromatography to give the pure ligand **3a**: white solid, 42% yield; mp: 141–142 °C; $[\alpha]_D^{27}$ −42.26 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.61 (d, $J = 6.4$ Hz, 3H), 2.21 (s, 3H), 3.06 (dd, $J = 6.4$ and 12.8 Hz, 1H), 3.34 (dd, $J = 4.8$ and 9.6 Hz, 1H), 3.42–3.47 (m, 1H), 3.67 (dd, $J = 4.8$ and 10.0 Hz, 1H), 3.96 (s, 2H), 4.57 (d, $J = 6.0$ Hz, 1H), 7.08–7.10 (m, 2H), 7.24–7.40 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 11.48, 36.10, 44.90, 57.48, 66.82, 76.82, 119.91 (q, $J_{CF} = 320$ Hz), 126.61, 128.02, 128.37, 128.61, 128.82, 137.16, 142.72; HRMS Calculated for $C_{19}H_{24}N_2O_3F_3S$ $[M+H]^+$ 417.1460, found: 417.1466.

12. *General procedure for the addition of phenylacetylene to aldehydes*: Under argon, chiral ligand (10 mol %, 0.025 mmol) was mixed in dry toluene (1.0 mL) at room temperature and stirred for 10 min. Then, Et_2Zn (10 wt % in hexane, 0.9 mL) and phenylacetylene (54 μL, 0.5 mmol) were added by syringe. After the mixture was stirred at room temperature for another 1 h, aldehyde (0.25 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. Then, the reaction was quenched with aqueous HCl (5%) and the mixture was extracted with ether (3 × 6 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography to give the product.
13. Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2655.